

Research and Innovation to Stop E-cigarette/Vaping in Young Adults Research Protocol

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I. Objectives

Using an efficient multiphase optimization strategy (MOST) complete factorial designed trial, we will examine the optimal contribution of promising components targeting vaping cessation (7-day point prevalence abstinence at 3-months) for young adults. A 2x2 factorial design will be used where all participants receive quitline-delivered phone counseling, and components to be tested are a digital intervention (with text-based cessation and online cessation support) and nicotine replacement therapy (NRT).

Research questions:

1. Which components and combinations of intervention yield the greatest success rates for exclusive vaping cessation among young adult exclusive e-cigarette users?
H1: The complete condition (NRT + digital) will yield significantly higher rates of cessation compared to the control condition (quitline only).
2. Does 8 weeks of nicotine replacement therapy (NRT) improve initial cessation outcomes relative to no NRT.
H2: Providing NRT will yield significantly higher quit rates compared to the No NRT condition.
3. Do tailored text-messages and online support during cessation improve initial cessation outcomes relative to no digital content? Are young adult vapers engaged with and satisfied with digital cessation tools?
H3: Digital support will yield significantly higher quit rates compared to no digital support.
H4: Higher engagement in digital content will be associated with higher cessation success rates.

II. Background and Rationale

Electronic cigarette (e-cig) “vaping”, while being promoted as a safer alternative to conventional cigarettes, has disproportionally attracted adolescents and young adults. E-cig use has increased dramatically in recent years, especially among youth, and are now the most commonly used tobacco product among this age group, yet little research has examined youth e-cig addiction, health effects, or strategies to help current young adult users quit.^{1,2,3,4} E-cig products continue to evolve rapidly, resulting in a product with increasing youth appeal and addictiveness, exposing youth to cardiovascular and pulmonary toxicants during a sensitive and critical time of development.^{5,6,7,8}

Regulatory and research efforts have largely focused on e-liquid flavors, which while important, do not appear to be the catalyst for the surge.⁹ Flavored e-cigs have been on the market since the late 2000s, but in a market saturated with these products, youth e-cig use was declining through 2017.¹ It was not until the proliferation of nicotine-salt based (NSB) e-cigs, like JUUL, that youth e-cig use increased by 135% to its current record high.³ Unlike previous e-cigs that relied on unprotonated, or “free-base” (FB) nicotine e-liquid, NSB devices use protonated forms.¹ Because this form of nicotine is not as harsh as the FB form, inhaling high doses of protonated nicotine is much more palatable.⁵ This allows “tobacco naïve” users to inhale high levels of nicotine at initiation, increasing their odds of becoming addicted, a problem drawing serious concern from parents, schools, health officials and regulators.⁵

There is now a wave of support and a need for research to develop an effective, scalable and easily accessible vaping cessation intervention. A previous feasibility study demonstrated the effectiveness a text-based program advertised via social media: approximately 70% of youth engaged in the program set a quit date and nearly 25% reported vaping cessation for at least a week during the 3-month follow-up.¹⁰ Based on this study and other tobacco cessation initiatives, we are confident in the ability of this project to obtain useful results without undue risk to human subjects. The American Heart Association also shares this belief, as evidenced by their funding of this project.

There are many potential benefits to be gained by this study. While individual participants may or may not benefit from participation, they could be aided in their attempts to quit vaping/e-cigarette use, however, this will be highly dependent on the individual. Society as a whole will benefit from this research program: by developing an effective e-cig cessation program, young adult use of e-cig products will decrease. Elimination of nicotine can have long term health benefits over the life course in the prevention of cardiovascular disease and cancer resulting in lower healthcare costs and overall increased quality of life.

III. Procedures

A. Research Design

Using an efficient multiphase optimization strategy (MOST) complete factorial designed trial, we will examine the optimal contribution of four promising components targeting vaping cessation (7-day point abstinence) for young adults: quitline-delivered phone counseling, text-based cessation, nicotine replacement therapy (NRT), and online cessation support. The proposed design is a complete factorial experiment (2^2), where the levels of these two independent components are systematically varied, or “crossed”, so that all possible combinations of component levels, or factors, are implemented across the 4 groups. Cessation outcomes will be assessed via online surveys at baseline- prior to the first coaching call- and 3-months following completion of the first coaching call.

B. Sample

For the RISE study, 1200 participants will be recruited for the baseline survey. We expect a 40% attrition to completing the first call and 30% attrition rate to the 3-month Qualtrics follow up survey. This total number of participants satisfies the 90% power and 0.10 for one-sided alpha for type I error rate to detect main effects odds ratios of 2.0 or greater (assuming a baseline quit rate of 15%). With this same sample size, we will also be well powered (power>80%) to detect smaller effects (OR=1.8).

Potential participants will be recruited by a recruitment firm using social media ads targeting young adults who vape and are interested in quitting. Specific eligibility for this study include:

- 1) Age 18-24: Adolescents and young adults are disproportionately affected by e-cig use.^{1,2,3,4} E-cigs are now the most commonly used tobacco product among this age group, yet little research has examined strategies to help current young adult users quit. Young adults are a priority age group for this intervention topic and the focus of this study.

- 2) **Not pregnant or breastfeeding:** because nicotine is a reproductive toxicant,¹¹ pregnant or breastfeeding individuals will not be eligible for the study. We will rely on self-report measures if a study participant were to become pregnant during the study. If a participant becomes pregnant during the study they will need to inform the Project Manager, Elizabeth Hustead, via email
- 3) **Current, exclusive e-cigarette use:** to determine if interventions are effective it is essential that participants exclusively use e-cigarettes and no other tobacco products
- 4) **Interest in quitting in the next 30 days:** in order to recruit potential participants, we need to recruit individuals who are ready to quit now
- 5) **Ownership of a smartphone device:** counseling and other intervention strategies will be delivered via text and digital media: without a smartphone, participants would be unable to access this content
- 6) **mental health conditions:** potential participants with schizophrenia and those with bipolar disorder who do not report that their condition is currently effectively managed will be excluded from the study. This is for two main reasons:
 - a. This intervention needs to be tested in a homogenous “healthy” population in order for us to test our hypotheses. It is industry standard for individuals with schizophrenia and bipolar disorder that is not effectively managed to be excluded from studies in order to achieve a homogenous population.
 - b. This is a low-touch intervention, it is critical that participants are adequately engaged in the intervention. Prior experience indicates that individuals with these conditions are unable to effectively participate in counseling phone calls and engage with the online content.
- 7) **NRT use exclusions:** individuals who have experienced a heart attack or stroke in the two weeks prior, or who have been diagnosed with rapid/irregular heartbeat or angina in the six months prior to taking the eligibility screener will be ineligible to participate.¹² This is because they would be unable to utilize NRT (nicotine replacement therapy) if they were randomized to that study arm.
- 8) **ability to speak and read English:** potential participants will need to be able to speak and read English in order to participate in the cessation counseling phone calls and interact with the online program materials.
- 9) **no other household members in study:** it is important that we do not enroll potential participants from the same household in order to prevent potential cross-contamination across treatment arms.

C. Measurement/Instrumentation

Measures for the RISE eligibility, baseline, and 3-month follow-up questionnaires were sourced from the Project ENDSmoking study¹³ and the Pennsylvania State E-Cigarette Dependence Index.¹⁴ Both measures are well established in the field of e-cigarette and tobacco cessation. Given emerging nature of e-cigarette research, detailed psychometrics for data collection of e-cigarette cessation are not yet publicly available.

D. Detailed study procedures

Step 1: Recruitment: A recruitment firm will recruit a national, nonprobability sample (n=576) of young adults using digital media platforms including but not limited to Facebook, Instagram, and TikTok. Recruitment firm will collect contact information and send potential participants the eligibility survey.

Step 2: Consent: Consent will be obtained via Qualtrics survey as a precursor to each of the three online surveys.

Step 3: Determining eligibility: Eligibility will be determined by the OSU research team via a Qualtrics survey. Criteria will include 1) age 18-24; 2) not pregnant, 3) current, exclusive e-cig use, 4) interest in quitting in the next 30 days; and 5) ownership of a smartphone device.

Step 4: Baseline survey: Eligible participants will be directed to a baseline Qualtrics survey. Consent will be obtained in this survey.

Step 5: Randomization: Upon verified completion of the baseline survey the participant will be randomized into 1 of 4 groups (2X2 fully crossed design) with the 2 factors being NRT (yes/no) and a digital cessation intervention (yes/no). At this time their pertinent study information will be shared with Optum via securely and automatically transfers files to and from FTP servers (FTPS/SSL); (SFTP/SSH).

Step 6: Coaching call 1: Participants will complete one 15-min session coaching session focused on focus on 5 “keys” for quitting: setting a quit date, conquering urges, addressing nicotine replacement needs, vape-proofing environment, and social supports. The first \$40 incentive will be distributed following the completion of call #1.

Step 7: Phone counseling, NRT, initiation of digital intervention

- 1) Using contact information provided by OSU, trained Optum cessation coaches will begin calling out to participants to complete the initial phone coaching call. All participants will receive 2 phone counseling sessions with a quit coach trained in vaping cessation. Coaches will be aware of the group assignment for each participant (NRT yes/no; digital yes/no) and will facilitate participants’ engagement in these interventions. Coaching call 1 will focus on 5 “keys” for quitting: setting a quit date, conquering urges, addressing nicotine replacement needs, vape proofing environment, and social supports.
- 2) NRT: The study will provide up to 8 weeks of nicotine replacement (NRT, patch, gum, and/or lozenge) to those randomly assigned to receive NRT (versus none). In this real-

world trial, coaches will be trained to assess vaping use and dose NRT taking into account use frequency, nicotine level, and participant preference, leveraging Optum's quitline standard protocols and best practice recommendations (e.g., combination therapy, patch plus gum or lozenge, may be offered to daily NSB users reporting symptoms of heavy nicotine dependence). NRT will be delivered to participants in 2 shipments, each following a coaching call that will include assessment of NRT use exclusions and dosing.

- 3) Digital Intervention: Text messaging and online multi-media content. Participants in the digital intervention condition will be enrolled into the text messaging and online course content following the first coaching call. The text program will start within 48 hours of coaching call 1 and will be tailored to participants' quit stage (e.g., preparing to quit, recently quit, relapsed, quit and stable). Texts will include education, tips, motivational messages, and assessment questions yielding tailored content. Text messages will continue for up to 90 days, but participants can opt out of the text messaging program at any time. At the start of the text messaging intervention participants will receive 1-2 messages per day. Frequency will change based on participant's quit status (those who have successfully quit receive fewer) and preferences. Participants can also initiate text messaging support by texting in a key word (such as "stress" or "crave") which will result in tailored messages being delivered. The self-paced online intervention will include education, motivational enhancement, quit planning, and journaling exercises and will include video and animated content tailored to the target audience of young adults who vape. The text program will send links to online course multimedia content to encourage engagement or the online content can be accessed directly.

Step 8: Coaching call 2: Coaching call 2 will occur approximately 2 weeks following call 1. Coaches will call participants soon after their proposed quit date. Content of the call will include assessment of quit status, re-setting the quit date for those who have not quit or providing relapse prevention guidance for those that have quit, reassessment of NRT use exclusions and dosing for second shipment (only for NRT group), and assessment of engagement in text messaging and online course and assistance accessing these if needed (only for digital intervention group).

Step 9: Follow up survey: Participants will be emailed a link to the Qualtrics survey. Up to 5 reminders will be sent to participants to aid in survey completion. The second and final \$40 incentive will be distributed following survey completion. Up to three email contact attempts will be made to distribute the survey link.

E. Internal validity

No major threats

Nationally representative sample w/ randomization

Through the use of observation over time: provides assurance that causal relationship to be observed is appropriate: see people vaping at beginning and not at the end: do we believe intervention is causative

External: generalizability: large sample, randomization to address confounding, nationwide sample

We are confident in the internal validity of the RISE study due to the longitudinal nature of data collection and the clear causality of e-cigarette cessation following our interventions. Additionally, due to the large sample size and randomization to address confounding, we are confident in stating that there are no major threats to external validity and that all possible precautions to prevent study bias have been taken.

F. Data Analysis

Analyses will examine the differences between the two levels of the intervention on the primary outcome, biochemically verified 7-day point prevalence abstinence (yes/no) assessed at 3-months; secondary analyses will examine self-reported abstinence at 3 months. Analyses will use ANOVA-style effect coding so that main effects can be estimated (on average across other factors). Due to the binary outcome, we will use logistic regression to estimate main effects and all two-way interactions. We expect a 70% retention rates so that a final sample (n=352 participants) will remain engaged at 3-month follow-up, we have 90% power and 0.10 for one-sided alpha for type I error rate to detect main effects odds ratios of 2.0 or greater (assuming a baseline quit rate of 15%). With this same sample size, we will also be well powered (power>80%) to detect smaller effects (OR=1.8).

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